REMARKS

Applicants have amended claim 1 to recite: "A compound 12 to 30 nucleobases in length comprising an at least 8 consecutive nucleobase portion of SEQ ID NO: 64, wherein said compound is 100% complementary to SEQ ID NO:17." Support for this amendment can be found, for example, in the specification at page 9, lines 3-34, page 84, lines 2-11, and original claim 10. Claims 15 and 16 are amended to delete "any of." Claim 18 is amended to recite "wherein each internucleoside linkage in said oligonucleotide is a phosphorothioate linkage." New claim 19 is added. Support for this amendment can be found, for example, at Example 15.

35 U.S.C. § 112, second paragraph – Indefiniteness

Claims 1-9, 11-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 1 is rejected over recitation of "12 linked nucleosides." Applicants have deleted this limitation, rendering this rejection moot. Claims 15 and 16 are rejected over recitation of "any of" a single sequence. Applicants have deleted the objected to phrase. Claim 18 is rejected over recitation of "each internucleoside linkage is a phosphorothioate linkage," which the Examiner views as ambiguous. Applicants have amended claim 18 to recite "each internucleoside linkage in said oligonucleotide is a phosphorothioate linkage," to clarify the limitation. In view of the above, Applicants request that the rejection of the pending claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. §§ 102(e) and 103(a) – Anticipation/Obviousness

The Examiner rejects claims 1-3, 7, 11 and 13-15 under 35 U.S.C. § 102(e), or in the alternative under 35 U.S.C. § 103(a), as anticipated or obvious over Mittman *et al.* (USPN 6,821,724). The Examiner asserts that Mittman discloses an antisense oligonucleotide 12-30 nucleobases in length comprising at least 12 linked nucleosides of SEQ ID NO: 64. *Office Action* at 4. The Examiner states that Applicants have the burden of "establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed." *Id.* Applicants respectfully traverse.

Without acquiescing to the Examiner's assertions regarding the disclosure of Mittman, and solely in the interest of advancing prosecution, Applicants have amended claim 1 to recite "A

compound 12 to 30 nucleobases in length comprising an at least 8 consecutive nucleobase portion of SEQ ID NO: 64, wherein said compound is 100% complementary to SEQ ID NO:17." According to the alignment provided by the Examiner in the Office Action, SEQ ID NO:2494 of Mittman is only 65% complementary to SEQ ID NO:64. Thus, it does not meet the limitation of claim 1, which requires that the compound comprise an at least 8 consecutive nucleobase portion of SEQ ID NO: 64, and be 100% complementary to SEQ ID NO:17.

Nor is it obvious to modify SEQ ID NO:2494 of Mittman to meet the limitations of claim 1, and those claims which depend therefrom or otherwise incorporate the limitations of claim 1. SEQ ID NO:2494 of Mittman is not directed to BCL2-associated x protein, but instead is targeted to M16362, a mouse opa repeat mRNA. *See Mittman* at Table 1. In view of the above, Applicants request that the Examiner withdraw the rejection of claims 1-3, 7, 11 and 13-15 under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) over Mittman *et al.*

35 U.S.C. §103(a) – Obviousness

The Examiner rejects claims 1-9 and 11-18 under 35 U.S.C. § 103(a) as unpatentable over Mittman *et al.* in view of Korsmeyer, Milner *et al.* and McKay *et al.* The Examiner relies upon Mittman as discussed above in the 102(e)/103(a) rejection, but states that Mittman does not disclose various features of the claims such as specific chemistries. *Office Action* at 6. The Examiner asserts that Korsmeyer discloses the inhibition of expression of SEQ ID NO:17 using antisense, while Milner discloses "methods of designing and testing antisense oligonucleotides." *Office Action* at 6. The Examiner asserts that McKay discloses various aspects of compositions and chemistry. Based on these disclosures, the Examiner concludes that:

> It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides between 12-20 nucleobases in length comprising at least 12 contiguous nucleobases of SEQ ID NO. 64 to inhibit the expression of SEQ ID No. 17, encoding the BCL2-associated x protein (BAX) in vitro, because Mittman teaches this antisense sequence.... *Office Action* at 7 (emphasis added).

Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness.

As discussed above, pending claim 1 recites "A compound 12 to 30 nucleobases in length comprising an at least 8 consecutive nucleobase portion of SEQ ID NO: 64, wherein said compound is 100% complementary to SEQ ID NO:17." According to the alignment provided by

the Examiner in the Office Action, SEQ ID NO:2494 of Mittman is only 65% complementary to SEQ ID NO:64. Thus, it does not meet the limitation of claim 1, which requires that the compound comprise an at least 8 consecutive nucleobase portion of SEQ ID NO: 64, and be 100% complementary to SEQ ID NO:17.

Nor is it obvious to modify SEQ ID NO:2494 of Mittman to meet the limitations of claim 1, and those claims which depend therefrom or otherwise incorporate the limitations of claim 1. SEQ ID NO:2494 of Mittman is not directed to BCL2-associated x protein, but instead is targeted to M16362, a mouse opa repeat mRNA. *See Mittman* at Table 1. The Examiner has not provided any evidence that even when combined with the teachings of Korsmeyer, Milner and McKay, one of skill in the art would arrive at an compound that meets the limitations of claim 1 based on SEQ ID NO:2494.

In addition, the Examiner's argument relies on the erroneous assertion that Milner discloses methods of "designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the expression of target nucleic acid of known sequence in vitro..." *Office Action* at 6 (emphasis added). Elsewhere, the Examiner asserts that "Milner et al and McKay teach the ability to design and assess antisense oligonucleotides...," and that "Milner teaches methods of designing and assessing antisense oligonucleotides...." *Office Action* at 7 and 8.

Applicants can find no disclosure in Milner regarding the design of antisense. Instead, Milner discloses a "simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence." *Milner* at Abstract. Milner does not disclose how to design antisense oligonucleotides, but rather how to screen oligonucleotides designed by others to determine which ones are likely to be effective *in vitro*. In fact, Milner teaches that "[w]e find no obvious features in the mRNA sequence or the predicted secondary structure that can explain the variation in heteroduplex yield," and that "[t]he sequence and predicted secondary structure of the mRNA give few clues as to what makes BG1 particularly amenable to duplex formation." *Milner* at Abstract and page 539, second column. Thus, far from providing guidance which would render the claimed invention obvious, Milner discloses that it is unpredictable which portions of a molecule are good targets for antisense. This supports Applicants' assertion that it

would not be obvious to modify the sequence of Mittman to arrive at a compound that satisfies the limitations of claim 1.

Thus, the Examiner has failed to establish a *prima facie* case of obviousness for at least the reason that the cited references, alone or in combination, do not teach or suggest every limitation of the pending claims. Mittman does not disclose a compound that meets the limitations of claim 1, and it would not be obvious to modify the sequence of Mittman directed to an unrelated mouse gene to arrive at the molecule of claim 1. Nor has the Examiner pointed to any portions of the other cited references which establish that it would be obvious to design a compound that satisfies the limitations of claim 1, since Milner actually teaches that it is unpredictable which portions of the target nucleic acid are good targets for antisense. In view of the above, Applicants respectfully request that the Examiner withdraw the rejection of the pending claims under 35 U.S.C. § 103(a) over Mittman *et al.* in view of Korsmeyer, Milner *et al.* and McKay *et al.*

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, the Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. The Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

Patents and Applications of Assignee

Applicants wish to draw the Examiner's attention to the following patent(s) or application(s) of the present application's assignee. Applicants encourage the Examiner to

review and monitor the prosecution of the following patent(s) and/or application(s) throughout the pendency of this application.

Patent/Serial No.	Title	Issued/Filed
09/908,147	Antisense modulation of BCL2-associated X protein expression	07-17-2001

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 4/3/08

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